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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,273	12/11/2000	Edwin A. Clark	2825.2004-001	3583

21005 7590 01/02/2003

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EXAMINER

GUNTER, DAVID R

ART UNIT PAPER NUMBER

1634

DATE MAILED: 01/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

09/735,273

Applicant(s)

CLARK ET AL.

Examiner

David R. Gunter

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☐ Responsive to communication(s) filed on \_\_\_\_.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☐ Claim(s) 12-17, 19 and 27-29 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 12-17, 19 and 27-29 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.  
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All b) ☐ Some \* c) ☐ None of:  
1. ☐ Certified copies of the priority documents have been received.  
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_.  
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892) 4) ☒ Interview Summary (PTO-413) Paper No(s). 10.
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4, 7. 6) ☐ Other: \_\_\_\_\_

**DETAILED ACTION**

1. Applicant's election of group II, claims 12-19, 27-29, and 35 in Paper No. 9, dated October 17, 2002 is acknowledged. Because applicant did not distinctly and specifically point out any supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. As summarized in the interview summary of paper 10, the applicant and the examiner have agreed that claims 18 and 35, originally included in group II, are distinct from the remainder of the claims of group II. Claims 18 and 35 have therefore been removed from consideration. Claims 12-17, 19, and 27-29 are under prosecution.

During the interview, the examiner required that an election of species be made by the applicant in regard to the list of metastatic conditions listed in claim 17. No such election has been made. In the interest of expediting prosecution of the case, the examiner has chosen to withdraw the requirement for an election of species.

***Claim Rejections - 35 USC § 112***

3. Claims 12-17, 19, and 27-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement

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requirements and whether undue experimentation would be required to make and use the claimed invention (see *In re Wands*, 858 F. 2d 731, 737, 8 USPQ 2d 1400, 1404, 1988). These factors include but are not limited to:

- a. Nature of the invention: The claims of the current application are drawn to a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of (a) obtaining a biological sample from a mammal to be tested; (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal; and (c) comparing the level determined in (b) with an appropriate control, wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition.

The claims further recite a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of: (a) obtaining a biological sample from a mammal to be tested; (b) determining the level of one or more gene products which regulates metastasis in one or more tumor cells in the mammal; and (c) comparing the level determined in (b) with an appropriate control; wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition.

- b. Breadth of the Claims: The claims as written are extremely broad for the following reasons:

- 1) The claims read on predicting the likelihood of development of a metastatic condition. The claims do not recite the nature of the likelihood of

development, how this increased or decreased likelihood is to be measured, or what constitutes a clinically or statistically significant change in the likelihood of developing a metastatic condition compared to a control. The claims read on a prediction made at any stage of the mammal's life, before the development of clinical samples, and potentially prior to birth if a sample is collected *in utero*. As broadly as written, the claims read on any prediction regarding development of a metastatic condition made at any point in the lifetime of a mammal.

2) The claims read on predicting the likelihood of development of a metastatic condition in any species of mammal. As broadly as written, the claims read on thousands of species of animals including rodents, humans, marine mammals, and cattle.

3) The claims read on detection of any metastatic condition resulting from a neoplasm of any tissue in a mammal. Tumors arising from different tissues possess significant differences in their progression, severity, and potential clinical outcomes.

4) The claims read on the testing of any biological sample. As broadly as written, the claims read on analysis of a tissue biopsy, blood sample, urine sample, or hair sample.

5) The claims read on determining the level of any gene product or combination of gene products that alter the actin cytoskeleton. The claims do not specifically recite the nature of the alteration of the cytoskeleton, or the manner in which the gene product induces this alteration. Any change in cell shape or size

requires an alteration of the cytoskeleton, as does movement of the cell, secretion of products by the cell, endocytosis, pinocytosis, exocytosis, cell division, apoptosis, and many types of transportation of substances from location to location within the cell. There is an large number of gene products which have the potential to either directly or indirectly affect any of these processes, and thereby alter the cytoskeleton.

As broadly as written, the claims read on the analysis of any of dozens of types of samples from any of thousands of species of mammal, for the detection of any one of hundreds of gene products, or any combination thereof, for the purpose of determining any level of change in the likelihood of developing any of hundreds of metastatic conditions.

c. Amount of Direction and Guidance: The specification teaches the use of multiple cell lines of known metastatic potential injected into nude mice (page 25). The specification further teaches the creation of several sublines of A375 cells which overexpress rhoC, rhoA, or GFP (page 28). The specification teaches numerous assays for proliferation, chemotaxis, and metastatic potential of the cell lines (page 28). The specification does not teach the collection or analysis of biological samples from other species of mammals, or from any species of mammal with a spontaneously-occurring metastatic condition.

d. State of the Prior Art / Level of Predictability in the Art: The prior art teaches numerous genes that demonstrate an altered level of expression in metastatic tissue. Suwa, et al., British Journal of Cancer 77(1):147-153, 1998 (hereinafter "Suwa"), for

example, teaches a statistically significant correlation between expression of the rhoC gene in pancreatic ductal adenocarcinoma and metastasis. However, Suwa also teaches that no such correlation exists between metastasis and expression of genes closely related to rhoC such as rhoA or rhoB (Suwa, abstract).

e. Existence of Working Examples: The specification teaches the use of multiple cell lines of known metastatic potential injected into nude mice (page 25). The specification further teaches the creation of several sublines of A375 cells which overexpress rhoC, rhoA, or GFP (page 28). The specification teaches numerous assays for proliferation, chemotaxis, and metastatic potential of the cell lines (page 28). The specification does not teach the collection or analysis of biological samples from other species of mammals, or from any species of mammal with a spontaneously-occurring metastatic condition.

f. Quantity of Experimentation Required: The claims are drawn to the prediction of the likelihood of the development of a metastatic condition in a mammal based on an increased level of expression of a gene that alter the actin cytoskeleton. In order to make and use the invention, one of skill in the art would be required to determine a particular metastatic condition and species of mammal for further study. The skilled artisan would then be required to collect biological samples from normal individuals and those suspected of developing a metastatic condition. The level of expression of hundreds of genes would have to be determined, in triplicate to insure accurate results, from all tissue samples. The skilled artisan would then be required to wait, perhaps several years, to evaluate the progression of the metastatic conditions in the tested mammals using some

form of objective and quantitative measuring system. If meaningful correlations between gene expression and the metastatic conditions can be derived, then the skill artisan can apply the assay to the specific condition assayed in the species of animal studied. In order to use the assay for any other condition, or in any other species of mammal, further validation of the assay will be required, which will entail several more years of study.

In view of the breadth of the claims, in view of the limited guidance provided by the specification, in view of the unpredictability of the art, in view of the level of experimentation required, the specification does not describe the claimed invention in such a way as to enable one of skill in the art to make and/or use the invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 12, 13, 16, 17, 19, 27, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suwa in view of Steeg, et al., USPN 5,049,662, filed October 13, 1987, issued September 17, 1991 (hereinafter "Steeg").

a. Claim 12 recites a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of: (a) obtaining a biological sample from a mammal to be tested; (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal; and (c) comparing the level determined in (b) with an appropriate control; wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition.

Suwa recites a method comprising the steps of: (a) obtaining a biological sample from a mammal to be tested (page 147, right column, third paragraph); (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal (page 148, left column, second and third paragraphs); and (c) comparing the level determined in (b) with an appropriate control (figure 2); wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition (page 149, right column, last paragraph; page 151, left column, first paragraph). The gene product analyzed by Suwa is RhoC (page 149, right column, first paragraph), a

gene known to be "involved in cytoskeletal organization" (page 147, left column, second paragraph).

The teachings of Suwa determine the level of gene expression in a biological sample, and correlate the level of expression to an increased likelihood of developing a metastatic condition. The teachings of Suwa are descriptive, however, and do not specifically teach that the method of Suwa could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Suwa as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time the application was filed. Assays for the prediction of metastatic potential of tumor cells based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Suwa in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential (Suwa, page 149, right column, last paragraph; page 151, left column, first paragraph). One of skill in the art would have been motivated to

use a predictive assay based on Suwa because "[m]etastasis ... remains a primary cause of death for patients with solid tumors" (Steeg, column 1, 13-15).

b. Regarding claim 13, Suwa teaches the embodiment in which the mammal is human (page 147, right column, third paragraph).

c. Regarding claim 16, Suwa does not specifically teach that the control is a sample from a normal mammal, but rather teaches that the control is normal tissue from the pancreas of the individual from whom the test sample is obtained. It would have been obvious to one of ordinary skill in the art that normal tissue derived from the same individual is a functionally equivalent control to normal tissue derived from a separate individual. As such, it would have been obvious to one of ordinary skill in the art to obtain control samples either from the same individual from whom the test sample was obtained or from a normal individual based on the availability of tissue and the demands of the design of the particular assay.

d. Regarding claim 17, Suwa teaches the embodiment in which the metastatic condition is pancreatic cancer (page 147, right column, third paragraph).

e. Regarding claim 19, Suwa teaches the embodiment in which the biological sample is a sample from a tumor in a mammal (page 147, right column, third paragraph).

f. Claim 27 recites a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of: (a) obtaining a biological sample from a mammal to be tested; (b) determining the level of one or more gene products which regulates metastasis in one or more tumor cells in the mammal; and (c) comparing the level determined in (b) with an appropriate control; wherein if the level

determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition.

Suwa recites a method comprising the steps of: (a) obtaining a biological sample from a mammal to be tested (page 147, right column third paragraph); (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal (page 148, left column, second and third paragraphs); and (c) comparing the level determined in (b) with an appropriate control (figure 2); wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition (page 149, right column, last paragraph; page 151, left column, first paragraph). The gene product analyzed by Suwa is RhoC (page 149, right column, first paragraph), a gene known to induce malignant transformation in NIH 3T3 cells (page 147, right column, first paragraph) and demonstrated by Suwa to be associated with the invasive characteristics of pancreatic cancer (page 151, left column, last paragraph).

The teachings of Suwa determine the level of gene expression in a biological sample, and correlate the level of expression to an increased likelihood of developing a metastatic condition. The teachings of Suwa are descriptive, however, and do not specifically teach that the method of Suwa could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Suwa as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time the application was filed. Assays for the prediction of metastatic potential of tumor cells

based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Suwa in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential (Suwa, page 149, right column, last paragraph; page 151, left column, first paragraph). One of skill in the art would have been motivated to use a predictive assay based on Suwa because "[m]etastasis ... remains a primary cause of death for patients with solid tumors" (Steeg, column 1, 13-15).

g. Claim 29 recites a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of: (a) obtaining a biological sample from a mammal to be tested; (b) determining the level of one RhoC gene product in one or more tumor cells in the mammal; and (c) comparing the level of RhoC gene product in an appropriate control; wherein if the level determined in (b) is greater than the level of the RhoC gene product in said control, then the mammal has an increased likelihood of developing a metastatic condition.

Suwa recites a method comprising the steps of: (a) obtaining a biological sample from a mammal to be tested (page 147, right column third paragraph); (b) determining

the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal (page 148, left column, second and third paragraphs); and (c) comparing the level determined in (b) with an appropriate control (figure 2); wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition (page 149, right column, last paragraph; page 151, left column, first paragraph). The gene product analyzed by Suwa is RhoC (page 149, right column, first paragraph).

The teachings of Suwa determine the level of gene expression in a biological sample, and correlate the level of expression to an increased likelihood of developing a metastatic condition. The teachings of Suwa are descriptive, however, and do not specifically teach that the method of Suwa could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Suwa as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time the application was filed. Assays for the prediction of metastatic potential of tumor cells based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Suwa in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential (Suwa, page 149, right column, last paragraph; page 151, left column, first paragraph). One of skill in the art would have been motivated to use a predictive assay based on Suwa because "[m]etastasis ... remains a primary cause of death for patients with solid tumors" (Steeg, column 1, 13-15).

6. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fleischmann, et al., The Journal of Urology, 149:268-271, 1993 (hereinafter "Fleischmann") in view of Steeg. Claim 14 recites a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of: (a) obtaining a biological sample from a mammal to be tested; (b) determining the level of one or more gene products selected from a list of approximately 31 specific genes recited in claim 14; and (c) comparing the level determined in (b) with an appropriate control; wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition.

Fleischmann recites a method comprising the steps of: (a) obtaining a biological sample from a mammal to be tested (page 268, right column last paragraph); (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal (page 269, left column, first paragraph); and (c) comparing the level determined in (b) with an appropriate control (table 2); wherein if the level determined in (b) is greater than the

level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition (page 269, right column, first paragraph). The gene product analyzed by Fleischmann is fibronectin (page 269, left column, first paragraph), a gene recited in the list in claim 14 (b).

The teachings of Fleischmann determine the level of gene expression in a biological sample, and correlate the level of expression to the likelihood of developing a metastatic condition. The teachings of Fleischmann are descriptive, however, and do not specifically teach that the method of Fleischmann could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Fleischmann as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time the application was filed. Assays for the prediction of metastatic potential of tumor cells based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Fleischmann in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential (Fleischmann, page 269, right column, first paragraph). One of skill in the art would

have been motivated to use a predictive assay based on Fleischmann because “[m]etastasis ... remains a primary cause of death for patients with solid tumors” (Steeg, column 1, 13-15).

In the teaching of Fleischmann, it is determined that a decreased level of gene expression correlates with an increased likelihood of developing a metastatic condition instead of the correlation between an increased level of gene expression and the increased likelihood of developing a metastatic condition as recited in claim 14. However, based on the findings of Fleischmann, it would have been obvious to one of ordinary skill in the art that a change in fibronectin expression correlates with the risk of developing a metastatic condition, and that the nature of the correlation, and thus the interpretation of the predictive assay, must be dependent on and consistent with the observed data in the descriptive assay of Fleischmann.

7. Claims 15 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suwa in view of Steeg in further view of Fleischmann.

a. Claim 14 recites a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of: (a) obtaining a biological sample from a mammal to be tested; (b) determining the level of one or more gene products selected from a list of approximately 31 specific genes recited in claim 14; and (c) comparing the level determined in (b) with an appropriate control; wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition. Claim 15 recites the additional limitation to claim 14 that the gene product is RhoC.

Fleischmann recites a method comprising the steps of: (a) obtaining a biological sample from a mammal to be tested (page 268, right column last paragraph); (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal (page 269, left column, first paragraph); and (c) comparing the level determined in (b) with an appropriate control (table 2); wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition (page 269, right column, first paragraph). The gene product analyzed by Fleischmann is fibronectin (page 269, left column, first paragraph), a gene recited in the list in claim 14 (b).

The teachings of Fleischmann determine the level of gene expression in a biological sample, and correlate the level of expression to the likelihood of developing a metastatic condition. The teachings of Fleischmann are descriptive, however, and do not specifically teach that the method of Fleischmann could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Fleischmann as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time the application was filed. Assays for the prediction of metastatic potential of tumor cells based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the

NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Fleischmann in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential (Fleischmann, page 269, right column, first paragraph). One of skill in the art would have been motivated to use a predictive assay based on Fleischmann because "[m]etastasis ... remains a primary cause of death for patients with solid tumors" (Steeg, column 1, 13-15).

In the teaching of Fleischmann, it is determined that a decreased level of gene expression correlates with an increased likelihood of developing a metastatic condition instead of the correlation between an increased level of gene expression and the increased likelihood of developing a metastatic condition as recited in claim 14. However, based on the findings of Fleischmann, it would have been obvious to one of ordinary skill in the art that a change in fibronectin expression correlates with the risk of developing a metastatic condition, and that the nature of the correlation, and thus the interpretation of the predictive assay, must be dependent on and consistent with the observed data in the descriptive assay of Fleischmann.

Suwa teaches the embodiment in which the gene product is RhoC (page 149, right column, first paragraph).

b. Claim 27 recites a method of predicting the likelihood of development of a metastatic condition in a mammal, comprising the steps of: (a) obtaining a biological

sample from a mammal to be tested; (b) determining the level of one or more gene products which regulates metastasis in one or more tumor cells in the mammal; and (c) comparing the level determined in (b) with an appropriate control; wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition. Claim 28 recites the additional limitation to claim 27 that the gene product is selected from a list of approximately 32 specific genes recited in claim 28.

Suwa recites a method comprising the steps of: (a) obtaining a biological sample from a mammal to be tested (page 147, right column third paragraph); (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal (page 148, left column, second and third paragraphs); and (c) comparing the level determined in (b) with an appropriate control (figure 2); wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a metastatic condition (page 149, right column, last paragraph; page 151, left column, first paragraph).

The teachings of Suwa determine the level of gene expression in a biological sample, and correlate the level of expression to an increased likelihood of developing a metastatic condition. The teachings of Suwa are descriptive, however, and do not specifically teach that the method of Suwa could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Suwa as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time

the application was filed. Assays for the prediction of metastatic potential of tumor cells based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14). It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Suwa in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential (Suwa, page 149, right column, last paragraph; page 151, left column, first paragraph). One of skill in the art would have been motivated to use a predictive assay based on Suwa because "[m]etastasis ... remains a primary cause of death for patients with solid tumors" (Steeg, column 1, 13-15).

Neither Suwa nor Steeg teach that the gene product to be analyzed is fibronectin. Fleischmann, however, recites a method comprising the steps of: (a) obtaining a biological sample from a mammal to be tested (page 268, right column last paragraph); (b) determining the level of one or more gene products which alter the actin-based cytoskeleton of one or more tumor cells in the mammal (page 269, left column, first paragraph); and (c) comparing the level determined in (b) with an appropriate control (table 2); wherein if the level determined in (b) is greater than the level of the gene product in the control, then the mammal has an increased likelihood of developing a

metastatic condition (page 269, right column, first paragraph). The gene product analyzed by Fleischmann is fibronectin (page 269, left column, first paragraph), a gene recited in the list in claim 14 (b).

The teachings of Fleischmann determine the level of gene expression in a biological sample, and correlate the level of expression to the likelihood of developing a metastatic condition. The teachings of Fleischmann are descriptive, however, and do not specifically teach that the method of Fleischmann could be applied to samples collected in the future in order to predict the likelihood of development of a metastatic condition in a mammal. However, the use of the descriptive teaching of Fleischmann as the basis for a predictive assay would have been obvious to those of ordinary skill in the art at the time the application was filed. Assays for the prediction of metastatic potential of tumor cells based on increased expression of specific genes were well known to those of ordinary skill in the art at the time the application was filed. Steeg, for example, teaches "an in vitro diagnostic kit for predicting the cancer metastatic potential of tumor cells" (column 1, lines 27-30). In the assay taught by Steeg, "[h]ybridization of the cDNA clone for the NM23 gene to cellular RNA has predicted metastatic potential in both animal experimental metastasis model systems and human cancer" (column 5, lines 11-14).

It would have been obvious to one of ordinary skill in the art at the time the application was filed to modify the assay of Fleischmann in order to form a diagnostic assay as taught by Steeg because of the demonstrated correlation between elevated gene expression and metastatic potential (Fleischmann, page 269, right column, first paragraph). One of skill in the art would have been motivated to use a predictive assay

based on Fleischmann because “[m]etastasis ... remains a primary cause of death for patients with solid tumors” (Steeg, column 1, 13-15).

In the teaching of Fleischmann, it is determined that a decreased level of gene expression correlates with an increased likelihood of developing a metastatic condition instead of the correlation between an increased level of gene expression and the increased likelihood of developing a metastatic condition as recited in claim 14. However, based on the findings of Fleischmann, it would have been obvious to one of ordinary skill in the art that a change in fibronectin expression correlates with the risk of developing a metastatic condition, and that the nature of the correlation, and thus the interpretation of the predictive assay, must be dependent on and consistent with the observed data in the descriptive assay of Fleischmann.

### *Conclusion*

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David R. Gunter whose telephone number is (703) 308-1701. The examiner can normally be reached on 9:00 - 5:00 M - F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones can be reached on (703) 308-1152. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-9212 for regular communications and (703) 308-8724 for After Final communications.

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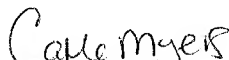
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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0198.



David R. Gunter, DVM, PhD  
December 29, 2002

  
CARLA J. MYERS  
PRIMARY EXAMINER